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California Environmental Protection Agency
Office of Environmental Health Hazard Assessment
P.O. Box 4010, MS-12B
Sacramento, California 95812-4010

Re: Hazard Identification Materials for Chlorpyrifos and n-Hexane

California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) is currently considering chlorpyrifos for possible listing under Proposition 65 based on the ***developmental toxicity*** endpoint. This new action is as a result of new data on developmental toxicity have become available since chlorpyrifos was previously considered for listing in 2008.

Beyond Pesticides is a national not-for-profit organization, with membership in California, that works to advance improved protections from pesticides and alternative pest management strategies that eliminate a reliance on toxic pesticides. We are writing on behalf of our California membership requesting that the agency list chlorpyrifos as a developmental toxin based on its undeniable association with developmental neurological interference in humans, especially children. In addition, since products from California are consumed across the national and around the world, the decision to list chlorpyrifos as a developmental toxin will have impacts beyond the state's borders. Further, in accordance with previous comments submitted to the agency, we are also calling for the revocation of state registrations of chlorpyrifos to protect vulnerable populations in the state. The agency is requesting data relevant to the potential developmental toxicity of chlorpyrifos, which we will outline below.

Agriculture is important to the California economy, and chlorpyrifos is used on a variety of crops grown in the state including almonds, cotton and citrus where over one million pounds of the chemical is used annually.[1] There have been several recent incidents involving chlorpyrifos drift from field applications that have put nearby workers and communities at risk, and recent air monitoring data reveal that chlorpyrifos residues are more than 18 times higher

[1] CDPR. 2017. Draft Evaluation of Chlorpyrifos as a Toxic Air Contaminant: Risk Characterization of Spray Drift, Dietary, and Aggregate Exposures to Residential Bystanders. Human Health Assessment Branch. Sacramento, CA.

than federal levels of concern.[2] Additionally, chlorpyrifos has the potential to contaminate surface and ground waters, further putting public health at risk.[3] Due to the chemical's toxicity, this environmental contamination only serves to underscore an urgent need for strong action against its continued use.

1. Chlorpyrifos is a neurological toxin hindering healthy neurological development

Chlorpyrifos is a cholinesterase inhibitor that binds irreversibly to the active site of an essential enzyme for normal nerve impulse transmission, acetylcholinesterase (AchE), inactivating the enzyme. California's recent assessment finds "potential health risks" for children and women of childbearing age from aggregate chlorpyrifos exposures, including spray drift.[4] The scientific evidence of neurotoxic dangers associated with chlorpyrifos exposure is extensive and consistent, particularly in children. Prenatal exposure is linked to tremors – involuntary contraction or twitching of muscles– in childhood. Researchers found that compared to all other children, those who had relatively high levels of prenatal chlorpyrifos exposure were significantly more likely to exhibit mild or mild to moderate tremor in one or both arms.[5]

Chlorpyrifos has been under scrutiny for decades as a result of its high potential to elicit adverse neurological developmental effects. The U.S. Environmental Protection Agency's (EPA) most recent assessment, which incorporated recommendations from the final report of a Scientific Advisory Panel (SAP), states there is "sufficient evidence that there are neurodevelopmental effects occurring at chlorpyrifos exposure levels below that required for AChE inhibition,"[6] and that EPA's current approach for evaluating chlorpyrifos's neurological impact is "not sufficiently health protective."[7] To come to this conclusion, EPA scientists rigorously reviewed data from the Columbia Children's Center for Environmental Health (CCCEH) study at Columbia University, which provided important information on the neurological outcomes of children exposed to chlorpyrifos. The study finds that children exposed to high levels of chlorpyrifos have mental development delays, attention problems, attention-deficit/hyperactivity disorder problems, and pervasive developmental disorders at three years of age.[8] High concentrations of chlorpyrifos in umbilical cord blood also correspond to a decrease in the psychomotor development and a decrease in the mental development in

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[2] CDPR. 2017. AIR MONITORING NETWORK RESULTS FOR 2016. Environmental Monitoring Branch. Sacramento, CA.

[3] USEPA. 2016. Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review. Office of Chemical Safety and Pollution Prevention. Washington DC.

[4] CDPR. 2017. Draft Evaluation of Chlorpyrifos as a Toxic Air Contaminant: Risk Characterization of Spray Drift, Dietary, and Aggregate Exposures to Residential Bystanders. Human Health Assessment Branch. Sacramento, CA

[5] Rauh VA, Garcia WE, Whyatt RM, et al. 2015. Prenatal exposure to the organophosphate pesticide chlorpyrifos and childhood tremor. *Neurotoxicology.* 51:80-6.

[6] USEPA. 2016. Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review. Office of Chemical Safety and Pollution Prevention. Washington DC.

[7] Ibid.

[8] Rauh VA. 2006. Impact of prenatal chlorpyrifos exposure on neurodevelopment in the first 3 years of life among inner-city children. *Pediatrics*. 118(6):e1845-59.

three year olds.[9] A similar 2012 study finds that children with high exposure levels of chlorpyrifos have changes to the brain, including enlargement of superior temporal, posterior middle temporal, and inferior postcentral gyri bilaterally, and enlarged superior frontal gyrus, gyrus rectus, cuneus, and precuneus along the mesial wall of the right hemisphere.[10]

As a result of the CCCEH data, EPA retained the 10X Food Quality Protection Act (FQPA) Safety Factor for all populations including infants, children and women of childbearing age while it continued its review. The 2016 SAP agreed with the overall conclusion of the CCCEH study –that there is *an association between chlorpyrifos prenatal exposure and neurodevelopmental outcomes in children*, even though the panel did not believe there is enough data on the relationship between cord blood concentrations at birth to exposures at and around the time of chlorpyrifos application to support its use in quantitative risk assessment.

2. Mechanism of chlorpyrifos neurotoxicity can occur at very low doses

The mechanism of the acute toxicity of organophosphates (OPs) like chlorpyrifos has been attributed to inhibition of acetylcholinesterase (AChE), but there is growing evidence that this may not account for all the long-term neurotoxic effects of OPs. Studies show that OPs can induce additional neurotoxic effects at very low levels concentrations below those demonstrated to inhibit AChE.[11] Some studies find that OPs concentration-dependently inhibited depolarization-evoked intracellular calcium concentration [Ca(2+)] –essential for proper neuronal development and function.[12] Others find that OP pesticides may influence the nervous system by disrupting the lipid profile of the nervous tissue; disrupting axonal transport (movement of mitochondria, lipids, synaptic vesicles, proteins, and other cell parts to and from neuron cells), and decreasing the number of nerve cells.[13]

EPA in its assessment also reviewed selected points of departure (PoD) and their use in the quantitative risk assessment. Data have shown that chlorpyrifos alters neuronal function

[9] Lovasi, GS, et al. 2011. Chlorpyrifos Exposure and Urban Residential Environment Characteristics as Determinants of Early Childhood Neurodevelopment. *Am J Public Health;* 101(1):63-70.
[10] Rauh VA, Perera FP, Horton MK, et al. 2012. Brain anomalies in children exposed prenatally to a common organophosphate pesticide. *Proc Natl Acad Sci U S A*. 109(20):7871-6.
[11] Androutsopoulos VP, Hernandez AF, Liesivuori J, Tsatsakis AM. 2013. A mechanistic overview of health associated effects of low levels of organochlorine and organophosphorous pesticides. Toxicology. 307:89-94.
[12] Meijer M, Hamers T, Westerink RH. 2014. Acute disturbance of calcium homeostasis in PC12 cells as a novel mechanism of action for (sub)micromolar concentrations of organophosphate insecticides. *Neurotoxicology*. 43:110-6.
[13] Roszczenko A, Rogalska J, et al. 2013. The effect of exposure to chlorfenvinphos on lipid metabolism and apoptotic and necrotic cells death in the brain of rats. *Exp Toxicol Pathol.* 65(5):531-9.

outside of, and unrelated to, the classical cholinesterase mechanism.[14,15,16] The agency determined that there is evidence that chlorpyrifos has effects below that which is observed for 10% red blood cell acetylcholinesterase (AChE) inhibition. However, regardless of the potential for multiple pathways of toxicity, the agency noted there remains high confidence in the current available and quantifiable evidence of neurological impact. EPA also stated that its revised analysis indicates "expected residues of chlorpyrifos on most individual food crops exceed the health-based 'reasonable certainty of no harm' safety standard under the Federal Food, Drug, and Cosmetic Act (FFDCA)." Additionally, the agency also points out that "risk from the potential aggregate exposure does not meet the FFDCA safety standard."

3. Chlorpyrifos disproportionately impacts vulnerable communities

Independent epidemiological data identify subpopulations that are disproportionately affected by chlorpyrifos exposures. Low-income African-American and Latino families, including farmworker families, continue to suffer the most, and this disproportionate impact creates an environmental justice. The UC Berkeley CHAMACOS team, studying organophosphate impacts on women and children in the Salinas Valley, CA, found that every 522 pounds of combined organophosphate pesticide applications within one kilometer of a pregnant woman's home correlates with a two point IQ loss in her children at seven years of age.[17] A 2014 study conducted by the UC Davis Mind Institute found that pregnant women who lived within a mile of agricultural fields where chlorpyrifos was sprayed had more than triple the chance of giving birth to a child with autism.[18] Data such as these illustrate the impact chlorpyrifos and other pesticides have on agricultural communities that are often low-income and minority communities.

As a result of the above evidence, we believe it is appropriate to recognize chlorpyrifos as a developmental toxin and inclusion on the Proposition 65 list. California now stands at a pivotal moment to take the lead in light of federal shortcomings, and take decisive action against this neurotoxic agent. Hundreds of our California members have already voiced opposition to the continued use of chlorpyrifos. The agency's own assessment identifies risks to children and women and childbearing age, consistent with EPA's and independent findings.

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[14] Lee I, Eriksson P, Fredriksson A, et al. 2015. Developmental neurotoxic effects of two pesticides: Behavior and biomolecular studies on chlorpyrifos and carbaryl. Toxicol Appl Pharmacol. 288(3):429-38.

[15] Androutsopoulos VP, Hernandez AF, Liesivuori J, Tsatsakis AM. 2013. A mechanistic overview of health associated effects of low levels of organochlorine and organophosphorous pesticides. Toxicology. 307:89-94.

[16] Meijer M, Hamers T, Westerink RH. 2014. Acute disturbance of calcium homeostasis in PC12 cells as a novel mechanism of action for (sub)micromolar concentrations of organophosphate insecticides. Neurotoxicology. 43:110-6.

[17] Gunier, RB, Bradman A, Harley K, et al. 2016. Prenatal Residential Proximity to Agricultural Pesticide Use and IQ in 7-Year-Old Children. Environ Health Perspect DOI: 10.1289/EHP504.

[18] Shelton, JF, Geraghty, E et al. 2014. Neurodevelopmental Disorders and Prenatal Residential Proximity to Agricultural Pesticides: The CHARGE Study. *Environ Health Perspect*; DOI:10.1289/ehp.1307044.

Chlorpyrifos is an incredibly neurotoxic organophosphate that has no place in modern agriculture as it poses dangers to farmworkers, farm families, especially vulnerable children,[19] and others living near agricultural areas.[20] There are alternatives available for farmers and other users in California, including organic production, that present less risk, and ensure that there is no disruption in food production and practices.

We urge the state to list chlorpyrifos as a developmental toxin and then quickly move forward to ban this dangerous chemical.

Sincerely,

Nichelle Harriott
Science and Regulatory Director

[19] Beamer, PI, et al. 2009 Farmworker children's residential non-dietary exposure estimates from micro-level activity time series. *Environ Int* ;35(8):1202-9.
[20] Harnly, ME, et al. 2009. Pesticides in dust from homes in an agricultural area. *Environ Sci Technol*;43(23):8767-74.